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In the land of the rising sun with the COP9 signalosome and related Zomes

Symposium on the COP9 signalosome, Proteasome and eIF3

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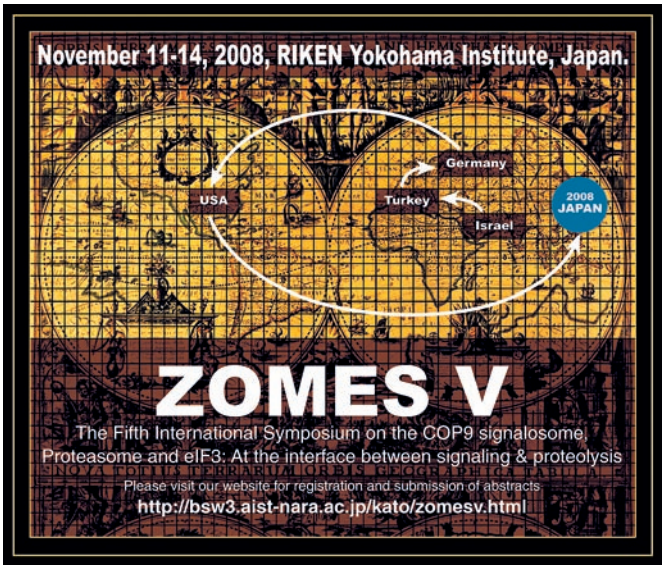

ZOMES V: The Fifth International Symposium on the COP9 signalosome, Proteasome and eIF3 took place between 11 and 14 November 2008, in Yokohama, Japan, and was organized by J-Y. Kato, M. Matsui, K. Iwai, K. Tanaka, M.Glickman, N. Wei & D. Chamovitz.

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See Glossary for abbreviations used in this article.

Introduction

Three macromolecular complexes—eIF3, the 26S proteasome lid and the CSN, referred to herein as 'Zomes'—share a unique molecular architecture and have an impact on proteins from synthesis to degradation. In higher eukaryotes, each complex consists of six subunits carrying a PCI domain and two subunits carrying an MPN domain, and each complex performs a distinct cellular function: eIF3 is involved in protein translation; the proteasome lid participates in protein degradation; and the CSN seems to have multiple functions related to the other two complexes, most of which regulate protein stability. However, despite years of research, the functional relationships between the three Zomes, their molecular architecture, the contribution of the individual subunits to the complexes, and the precise function and regulation of each have remained poorly understood. Aspects of these questions were discussed at Zomes V: The Fifth International Symposium on the COP9 signalosome, Proteasome and eIF3, which brought together more than 100 investigators from diverse fields working with various biological systems. Here, we highlight some of the main issues that were discussed at the conference.

Analogy and homology in Zomes molecular architecture

Among the three Zomes, the proteasome lid and the CSN share the highest homology (Fig 1): for each subunit of the proteasome lid, there is a paralogous subunit in the CSN complex. For example, Csn5 and Rpn11 are particularly close paralogues of one another, with both having a catalytic metal binding metalloprotease motif, MPN+/JAMM, which is responsible for the isopeptidase activity of each intact complex. Functionally, Rpn11 provides ubiquitin deconjugating activity to the proteasome, whereas Csn5 removes the ubiquitin-like protein Nedd8/Rub1 from the cullin subunit of cullin RING E3 ligases in a process called deneddylation (Cope & Deshaies, 2003). The metalloprotease motif is absent in eIF3 subunits. At the meeting, E. Isono and C. Schwechheimer (Munich, Germany) presented data on the *Arabidopsis* deubiquitinating enzyme AMSH3, which is a distantly related MPN+ protein, showing that complex assembly

Glossary

3T3	hypertriploid mouse fibroblast cell line
AMSH3	associated molecule with the Src homology 3 domain of signal transducing adaptor molecule
APC	adenomatous polyposis coli
ATM	ataxia-telangiectasia mutated
Cand1	cullin-associated and neddylation-dissociated 1
Cdc34	cell-division cycle 34
CDK	cyclin-dependent kinase
Ci^{155}	cubitus interruptus long isoform (155 kDa)
Cop1	constitutive photomorphogenesis 1
CRL	cullin-RING-E3 ligase
CSA	Cockayne syndrome A
CSN	COP9 signalosome
Cul	cullin
DDB2	damage-specific DNA binding protein 2
eIF3	eukaryotic initiation factor 3
Fbl12	F-box and leucine-rich repeat protein 12
Fbw7	F-box and WD-40 domain protein 7
HECT	homologous to E6-associated protein carboxyl terminus
HEK293T	human embryonic kidney 293 cells that stably express the large T-antigen of simian virus 40
Hh	Hedgehog
Hul5	Hect ubiquitin ligase 5
IκB	inhibitor of κ light polypeptide gene enhancer in B-cells
Ink4a	inhibitor of cyclin-dependent kinase 4 alternative reading
JAMM	Jun-activating binding protein/marapsin/Mov34 metalloenzyme
KIP2	cyclin-dependent kinase-inhibiting protein 2
Knd1	*Schizosaccharomyces pombe* orthologue of Cand1
Lag2	longevity-assurance gene 2
LSH1	light-dependent short hypocotyls 1
MEF	mouse embryonic fibroblast
Mlf1	myeloid leukaemia factor 1
MPN	Mpr1–Pad1–amino terminal
Nedd8	neural precursor cell expressed, developmentally downregulated 8
PAN	proteasome-regulatory ATPase complex in archaea
PCI	proteasome, COP9, eukaryotic initiation factor 3
Pcl5	Pho85 cyclin
PIC2	protein interacting with COP9
Rbx1	ring-box 1
RING	really interesting new gene
Rpn	proteasome regulatory particle, non-ATPase-like
Rpt	proteasome regulatory particle, ATPase-like
Rub1	related to ubiquitin 1
SCF	S-phase kinase-associated protein 1-cullin 1-F-box
Skp	S-phase kinase-associated protein
Slimb	supernumerary limbs
TNF-α	tumour necrosis factor-α
TrCP	transducin repeat-containing protein
Ubc	ubiquitin-conjugating enzyme
Ubp6	ubiquitin-specific protease 6
Ura3	uracil auxotrophic
Usp15	ubiquitin-specific protease 15

is not necessarily a prerequisite for the isopeptidase activity of all MPN+ proteins.

Despite the importance of these complexes and an abundance of protein-interaction studies, so far there is little information about the structural organization of their subunits. M. Sharon (Rehovot, Israel) and C. Robinson (Cambridge, UK) presented a subunit-interaction map of an active recombinant CSN complex, which they obtained through novel mass spectrometry. They proposed that the CSN is organized into symmetrical four-subunit modules that are bridged by interaction between Csn1 and Csn6. In this model, Csn2 and Csn5—which respectively bind to and deneddylate cullins—are peripheral and in close proximity to one another (Sharon *et al*, 2009).

Comparisons of the proposed CSN map with the existing maps of the regulatory lid and eIF3 show interesting similarities and differences between the three Zomes (Fig 1). In all three modular complexes, the MPN subunits interact directly with each other, and Csn5 and Rpn11 share similarly peripheral locations in both the proteasome lid and the CSN. Surprisingly, despite the one-to-one correspondence between paralogue subunits, the overall architecture of the CSN and the proteasome lid differs in terms of subunit positioning (Fig 1). For example, the two modules of the CSN and the proteasome lid are not connected by paralogous subunits (Csn1–6 and Rpn3–5, respectively), and the position of the paralogous subunits Csn2 and Rpn6 does not seem to be conserved.

D. Chamovitz (Tel Aviv, Israel) presented the crystal structure of CSN7, which was the first crystallized PCI subunit (Dessau *et al*, 2008). He presented a model in which PCI subunits are essential both for complex assembly and for interactions with MPN subunits, other counterparts and possibly even nucleic acids.

Unlike the CSN, which is an autonomous complex, the proteasome lid is a subcomplex of the 26S proteasome megacomplex. At the centre of this megacomplex is the catalytically active core particle 20S, which consists of four stacked heptameric rings. The rings are formed from two subunit types: structural α-subunits that form the outer two rings, and β-subunits that form the inner rings and are predominantly responsible for the catalytic activity of the core. The distal faces of the 20S associate with the regulatory particle 19S, which comprises a 'base' subcomplex that interacts with the 20S and the proteasome lid subcomplex (Glickman *et al*, 1999). The base consists of six homologous AAA-ATPase Rpt subunits that form a hexameric ring, two large proteins called Rpn1 and Rpn2, and the ubiquitin-binding proteins Rpn10 and Rpn13. Immediately following substrate binding to the proteasome, the deubiquitinating enzyme Rpn11 and the proteasome-attached protein Ubp6 remove ubiquitin chains from the substrate, while it is unfolded by the ATPases. In a yeast genetic screen, D. Kornitzer (Haifa, Israel) identified the involvement of Hul5, which is a HECT-type E3 ubiquitin ligase, in substrate processing before degradation. In the absence of Hul5 or in ATPase mutants such as *rpt2* reduction-of-function, a partly degraded processing product of the Ura3–Pcl5 fusion accumulates. Acting as an E4 ligase, Hul5 extends polyubiquitin chains on substrates (Crosas *et al*, 2006), presumably extending their residency in the proteasome, thereby providing more time for the substrate to be unfolded.

New aspects of the interaction between the 20S core particle and the 19S regulatory particle in eukaryotes were revealed at the meeting. Two groups used electron-microscopy imaging and modelling systems to elucidate the structure of the 26S proteasome. S. Nickel and W. Baumeister (Martinsried, Germany) were able to outline the boundaries of the hexameric AAA-ATPase module in the base of the regulatory complex, which can vary in both position and orientation relative to the 20S core particle. This observation is in agreement with the 'wobbling' model proposed previously to explain

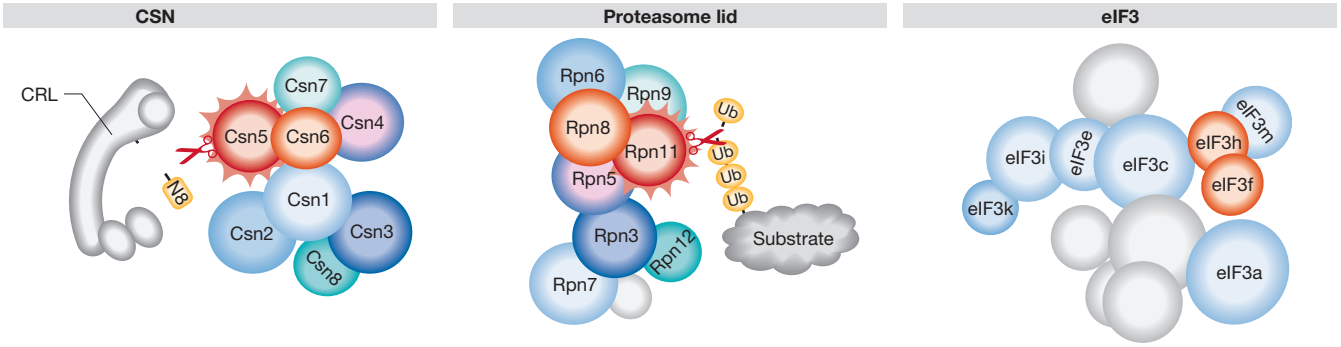

Fig 1 | Structural organization of the Zomes. The subunit organization map of the CSN (left), the 19S proteasome lid (middle) and eIF3 (right) are coloured according to the signature domains: PCI paralogous subunits are shown in variations of blue and MPN subunits are shown in variations of red. Scissors represent Csn5 and Rpn11 isopeptidase activities. The models were drawn according to Sharon *et al* (2006), Zhou *et al* (2008) and Sharon *et al* (2009). CRL, cullin-RING ligase; CSN, COP9 signalosome; eIF3, eukaryotic initiation factor 3; MPN, Mpr1–Pad1–amino terminal; N8, Nedd8; PCI, proteasome, COP9, eukaryotic initiation factor 3; Rpn, proteasome regulatory particle, non-ATPase-like; Ub, ubiquitin.

the role of 19S in opening the gate in the α-rings of 20S to allow substrate access to the catalytic degradation chamber (Smith *et al*, 2007). P. daFonseca and E. Morris (London, UK) showed radial displacements of the 20S subunits on 19S binding, leading to the opening of a channel into the 20S core, which might help to control the proteolytic activity of the proteasome. They also fitted a homology model of the AAA-ATPase domains of the Rpt subunits into a position that was adjacent to the 20S core, although tilted and offset from its central axis, and proposed that the 20S–Rpt and the archaeal 20S–PAN complexes show similar architecture.

The Rpn1 and Rpn2 subunits, which might coordinate the binding of ubiquitin-like domains to the yeast proteasome, are not conserved in archaea. Their location in the yeast proteasome is unknown, although they are generally assumed to be located distally to the ATPase ring, alongside Rpn10. M. Glickman (Haifa, Israel) described results showing that Rpn1 and Rpn2 form parallel but individual rings stacked on top of each other, creating a funnel-like structure above the 20S, which is surrounded by the ATPase ring (Rosenzweig *et al*, 2008). The three models presented at Zomes V, which are mentioned above, indicate interactions between the ATPases and the 20S, although the location of Rpn1/Rpn2 is still under discussion.

Interaction between Zomes

Not all eukaryotic genomes encode a full set of eIF3, proteasome lid and CSN subunits; however, the sequence similarity between several Zomes subunits raises the possibility of promiscuity in the incorporation of certain subunits into more than one complex. In addition, physical and genetic interactions between Zomes have been documented (Wei *et al*, 2008), although the functional significance of these cross-complex interactions and whether they represent a supercomplex are still unclear. E. Pick (Tivon, Israel), in collaboration with Glickman, showed that the yeast 26S proteasome co-purifies with deneddylation activity, which they attributed to an association between the proteasome and the CSN. Similarly, A. Kisselev (Hanover, NH, USA) presented biochemical evidence for a supercomplex containing the 26S proteasome, ribosomes, eIF3, other translation-initiation and elongation factors, and RNA-binding proteins in mammalian cells. D. Wolf (La Jolla, CA, USA) similarly reported that eIF3 co-purifies with the proteasome 19S regulatory complex, translation-initiation factors and ribosomes in *Schizosaccharomyces pombe*.

Biochemical studies of the CRLs and the CSN

CRLs comprise multisubunit E3 ligases containing the same catalytic core, but using distinct substrate-recognition modules nucleated around a cullin scaffold protein (Petroski & Deshaies, 2005). The substrate-recognition subunits of CRL complexes represent large families of proteins, such that the potential number of CRLs is staggering. One crucial question is whether all of these proteins function as authentic CRL subunits. For example, there are currently no simple rules to predict whether a given F-box protein can assemble into a functional SCF complex. Wolf reported that the sequence of the F-box dictates not only Skp1 but also Cul1 binding. In particular, a conserved proline residue in the F-box sequence is crucial for Cul1 binding (Fig 2).

At Zomes V, the diverse and crucial functions of SCF complexes in various cellular and biological processes such as cell signalling, differentiation and cell-cycle progression, were illustrated for various model systems. G. Serino (Rome, Italy) identified a new, light-induced F-box protein in *Arabidopsis*, known as PIC2, which might target the degradation of LSH1, a nuclear factor involved in the phytochrome-mediated light response. K. Nakayama (Kukuoka, Japan) illustrated the crucial role of SCF^{Skp2} and SCF^{Fbw7} in cell-cycle entry and exit from the resting G0 state *in vivo*, using T cells as a model system. Nakayama showed that the SCF^{Skp2}/p27 system is crucial for cell-cycle entry, whereas SCF^{Fbw7} promotes cell-cycle exit by triggering degradation of cell-cycle activators. Regulation of osteoblast differentiation by a new SCF^{Fbl12} complex was reported by T. Chiba (Tsukuba, Japan), who showed that this complex triggers the degradation of $p57^{KIP2}$, which is an inhibitor of the cyclin/CDK complex.

Nedd8 activates CRLs by triggering a conformational change of the carboxy-terminal part of the cullin that frees Rbx1, allowing it to adopt a variable conformation that brings the activated E2 enzyme in close proximity to the substrate (Fig 2; Duda *et al*, 2008). K. Wu and Z.K. Pan (New York, NY, USA) showed that Ubc5-dependent monoubiquitination of Cul1 can activate $SCF^{\beta\text{-}TrCP}$ and

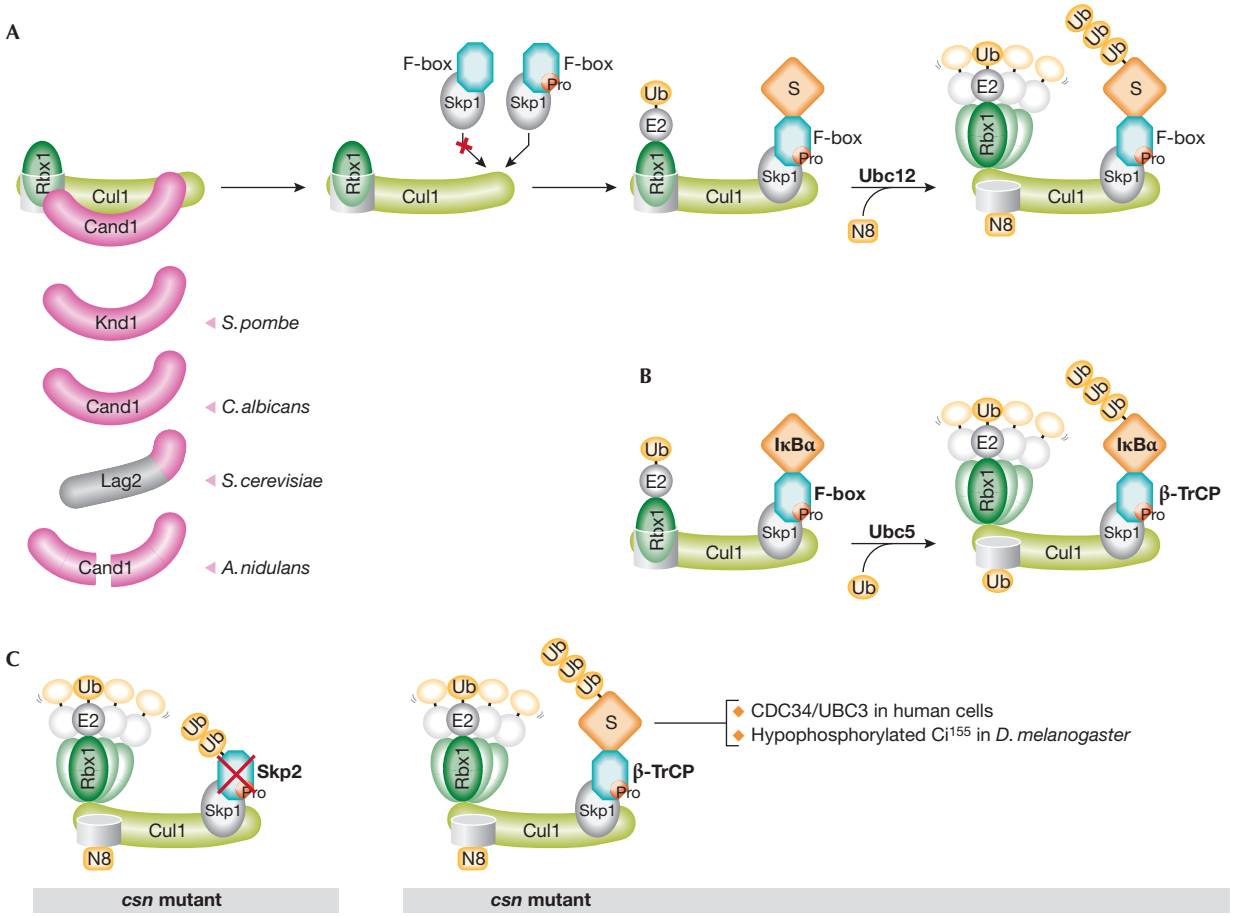

Fig 2 | SCF assembly and activation. (**A**) Cand1 and homologues in lower eukaryotes (purple). A conserved proline (Pro) residue in the F-box sequence dictates SCF assembly. SCF activation through neddylation is triggered by conformational changes of the carboxy-terminal region of Cul1 that free Rbx1 and thereby stimulate ubiquitination. (**B**) Ubc5-mediated monoubiquitination of Cul1 can similarly activate the $SCF^{\beta\text{-}TrCP}$ complex and trigger IκBα ubiquitination. (**C**) SCF^{Skp2} and $SCF^{\beta\text{-}TrCP}$ are not similarly affected by loss of the *csn*. Skp2 is highly unstable in *csn* mutants, whereas β-TrCP is only slightly affected. *A. nidulans*, *Aspergillus nidulans*; *C. albicans*, *Candida albicans*; Cand1, cullin-associated and neddylation-dissociated 1; Cdc34, cell-division cycle 34; *Csn*, COP9 signalosome; Cul cullin; *D. melanogaster*, *Drosophila melanogaster*; IκBα, inhibitor of κ light polypeptide gene enhancer in B-cells α; Knd1, *Schizosaccharomyces pombe* orthologue of Cand1; Lag2, longevity-assurance gene 2; N8, Nedd8; Rbx1, ring-box 1; S, substrate; *S. cerevisiae*, *Saccharomyces cerevisiae*; *S. pombe*, *Schizosaccharomyces pombe*; SCF, S-phase kinase-associated protein 1-cullin 1-F-box; Skp, S-phase kinase-associated protein; TrCP transducin repeat-containing protein; Ubc, ubiquitin-conjugating enzyme; Ub, ubiquitin.

mimics, to a certain extent, cullin neddylation, which is consistent with the observations of Duda and colleagues (Fig 2). By using an *in vitro* reconstituted system, Wu further showed that Ubc5 and Ubc3/Cdc34 cooperate in SCF-mediated ubiquitination of IκBα. Indeed, Ubc5 primes IκBα by monoubiquitination, allowing Cdc34 to elongate polyubiquitin chains.

E. Bianchi (Paris, France) reported that Ubc3/Cdc34 is degraded by ubiquitin-dependent proteolysis in human cells with compromised CSN function, in a similar manner to other SCF components such as Skp2. In contrast to Skp2, however, protein levels of the F-box protein β-TrCP are only moderately reduced after inactivation of *csn*. Consequently, Bianchi showed that the $SCF^{\beta\text{-}TrCP}$ complex is still active in *csn*-depleted cells, and targets Ubc3/Cdc34 and IκBα for proteasomal degradation. Similarly, J. Wu (Taipei, Taiwan) showed that *csn* mutants incorrectly respond to Hh in the developing *Drosophila* wing by inappropriately degrading the transcription factor Ci^{155}. Hh inhibits the kinases targeting Ci^{155} to the $SCF^{\beta\text{-}TrCP/Slimb}$ complex; therefore, Ci^{155} is stable with intermediate and high levels of Hh signalling, but is highly unstable with low-level Hh signalling. However, Wu noticed that $SCF^{\beta\text{-}TrCP/Slimb}$ targets Ci^{155} degradation at intermediate levels of Hh signalling in *csn* mutants, indicating that hypophosphorylated Ci is mistaken for $SCF^{\beta\text{-}TrCP/Slimb}$ substrate in the mutant. How does the CSN prevent Ci degradation? The answer is unclear; however, irreversible neddylation of Cul1, as observed in *csn* mutants, might augment the processivity of multiubiquitination by the $SCF^{\beta\text{-}TrCP/Slimb}$, and compensate for the low-affinity interaction between hypophosphorylated Ci^{155} and β-TrCP. Alternatively, CSN-associated deubiquitinating enzymes might counteract spurious ubiquitination of Ci^{155}, as was shown, for example, by M. Naumann (Magdeburg, Germany) in the case of IκB in TNF-α-treated cells.

Naumann reported further that Usp15 might regulate other IκB family members such as IκBβ and IκBε. Similarly, W. Dubiel (Berlin, Germany) showed that Usp15 controls $SCF^{\beta\text{-}TrCP1}$-mediated β-catenin destruction, by counteracting ubiquitin-mediated degradation of APC.

Currently, little is known about the molecular mechanisms that regulate CSN–CRL interactions. Importantly, two CRL complexes that are involved in DNA repair—$CRL4^{CSA}$ and $CRL4^{DDB2}$—were previously shown to associate dynamically with the CSN (Groisman *et al*, 2003). In particular, ultraviolet irradiation was shown to induce dissociation of $CRL4^{DDB2}$ from the CSN and its activation through Cul4 neddylation. R. Groisman (Villejuif, France) reported that Csn1 and Csn7 are phosphorylated upon ultraviolet irradiation, probably by the DNA damage-induced ATM kinase. Interestingly, cells expressing a non-phosphorylated version of Csn1 showed defects in DNA repair and ultraviolet-induced apoptosis. However, the association of the CSN lacking the Csn1 phosphorylation site with $Cul4^{CSA}$ and $Cul4^{DDB2}$ was unaffected. In addition to $Cul4^{CSA}$ and $Cul4^{DDB2}$, the CSN might regulate other CRL complexes. Consistent with this possibility, L. Pintard (Paris, France), together with M. Tyers (Toronto, Canada) and M. Peter (Zurich, Switzerland), presented a systematic proteomic analysis of the CSN in HEK293T cells by analysing immunoprecipitates of six different CSN subunits. Intriguingly, most of the CSN-interacting CRLs identified in this study have been implicated in DNA metabolism and include $Cul4^{CSA}$ and $Cul4^{DDB2}$, suggesting that specific functional subsets of CRLs are in dynamic association with the CSN.

The role of Cand1 in CRL regulation was also discussed. Cand1 sequesters cullin–Rbx1 heterodimers away from substrate-recognition modules and prevents cullin neddylation by steric hindrance (Hotton & Callis, 2008). Wolf reported the identification of a Cand1 homologue in *S. pombe* known as Knd1 and observed that the stability of the F-box protein is unaltered in knd1-deleted strains, indicating that Cand1 is required only to recycle substrate-recognition modules. The budding yeast genome does not contain a direct homologue of Cand1. However, using bioinformatics tools, K. Hoffman (Friedrich, Germany) ascertained that the *Saccharomyces cerevisiae* protein Lag2 contains a small region with notable similarities to the β-hairpin motif of Cand1, which interacts with Cul1 in mammalian cells. E. Siergiejuk, T. Kurz and M. Peter (Zurich, Switzerland) confirmed the observation made by Hofmann and showed that Lag2 specifically binds to Cdc53 in a neddylation-dependent manner. Overexpressing Lag2 in a neddylation-deficient strain severely impaired cell viability, and this phenotype was suppressed by mutation of the β-hairpin, providing functional evidence that Lag2 is an SCF inhibitor *in vivo*. N. Sela and D. Kornitzer (Haifa, Israel) showed that overexpression of the *Candida albicans* Cand1 homologue in budding yeast carrying *C. albicans* Cul1 is toxic, and even more so in a neddylation-deficient strain. However, in *C. albicans* itself, Cand1, although not essential, promotes SCF activity. In *Aspergillus nidulans*, Cand1 inactivation results in severe phenotypes, as illustrated by G. Braus (Göttingen, Germany), who also showed that the functions of Cand1 are split between two genes that resemble the mammalian amino-terminal and carboxy-terminal parts of Cand1 (Fig 2).

Zomes in development and cancer

The loss of regulation of the CSN and eIF3 complexes has a crucial role in tumorigenesis. J. Hershey (Davis, CA, USA) showed that overexpression of eIF3a, eIF3b, eIF3c, eIF3h or eIF3i subunits causes immortal 3T3 cells to become malignant. eIF3h is a non-conserved subunit that forms part of the functional core of eIF3; it is highly expressed in many cell lines, and might have an oncogenic role in colorectal cancer (Zhang *et al*, 2008). Overexpression of eIF3h malignantly transforms immortal 3T3 cells; conversely, reducing eIF3h levels in breast and prostate cancer cell lines by short-interfering RNA methods reduces their proliferation rates, indicating the importance of the tight regulation of translational initiation.

Deregulation of the CSN could also affect diverse cellular functions that are crucial for tumour development. At Zomes V, N. Wei (New Haven, CT, USA) showed that Csn8 has a crucial role in cell-cycle re-entry from quiescence in T cells and in MEF cells. Wei showed that the CSN complex can be recruited to cell-cycle genes by chromatin immunoprecipitation, suggesting that the CSN might have a direct role in transcriptional regulation. Similarly, J. Kato (Nara, Japan) showed that the mouse *Ink4a* gene immunoprecipitates with Csn5 from bone marrow. These findings tie into the proposal put forward by Chamovitz that CSN PCI proteins have DNA-binding activity.

Unlike Csn8, a significant fraction of Csn5 accumulates outside the CSN complex (Wei *et al*, 2008). Knockdown of *csn5* in cultured cells predominantly affects the level of free Csn5, rather than the levels in the CSN holocomplex (Wei & Deng, 2003). R. Pardi (Milan, Italy) found that *csn*-knockdown hepatocytes underwent spontaneous and stress-induced apoptosis, with a strong selection pressure for cells that did not delete *csn5*. *csn5*-knockout livers showed macroscopic structural alterations resembling macronodular cirrhosis. In models of injury-induced liver regeneration, conditional *csn5* inactivation leads to arrest in the G2/M phase, and to a 'constitutive DNA damaged' phenotype. It was therefore suggested at the meeting that the 'DNA-damaged' phenotype resulting from defective function of the CSN could be constitutive in tissues with a high mitotic index, and might be inducible by environmental stimuli in homeostatically quiescent cells or tissues. The findings of Pardi were in agreement with those of Schwechheimer, who reported that *Arabidopsis* CSN mutants are delayed—if not arrested—in the G2 phase, probably owing to the activation of the DNA damage-response pathway (Dohmann *et al*, 2008).

The involvement of Csn3 in tumorigenesis was reported by N. Yoneda-Kato (Nara, Japan), who showed that Mlf1 counteracts p53 degradation by inhibiting its E3 ligase Cop1 through Csn3 (Yoneda-Kato & Kato, 2008). Deregulation of Mlf1 owing to aberrant genetic alterations promotes oncogenic transformation. Interestingly, D. Xirodimas (Dundee, UK) showed that the regulation of p53 under nucleolar stress involves the neddylation of ribosomal proteins.

Concluding remarks

This biannual conference brought together Zomes' investigators from diverse fields using model systems ranging from plants to humans, and proved to be a stimulating meeting. Despite ongoing research efforts, questions remain unanswered at every level. The functional significance of the interaction between Zomes is still unclear. Similarly, the molecular mechanisms regulating these complexes and connecting their function to other cell events are poorly understood. In particular, the mechanisms controlling the interaction between the CSN and CRL complexes await further investigation. We hope that more light will be shed on these and other issues at the ZOMES VI meeting, which is planned for 2010 in Israel.

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